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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,617	03/16/2007	Anita Mehta	RLL-292US	6306

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EXAMINER	
BAEK, BONG-SOOK	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
11/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,617	MEHTA ET AL.	
	Examiner	Art Unit	
	BONG-SOOK BAEK	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2* is/are allowed.

6)☒ Claim(s) *1 and 3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/19/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-3 are currently pending. Claims 4-17 have been canceled.

Election/Restrictions

Applicants' election of group I (claims 1-3) and election of a species of formula I wherein Ar is phenyl; R_1 is OH; R_2 is phenyl; W is $(CH_2)_p$, where p is zero; X is oxygen, Y is CH_3; R_5, R_3 and R_6 are hydrogen; and R_4 is benzyl, in the reply filed on 9/10/2008 are acknowledged. The election was made without traverse.

Claims 1-3 are under examination in the instant office action. The elected species is free of prior art, thus examination has been extended to the full scope.

Priority

The instant application is a 371 of PCT/IB03/01333 filed on 04/10/2003.

The earliest effective U.S. filing date afforded the instantly claimed invention has been determined to be 04/10/2003.

Information Disclosure Statement

A signed and initialed copy of the information disclosure statement filed on 3/19/2007 is enclosed in this action.

Objection to Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract is required on a separate sheet.

Claim objections

Claim 1 is objected because of the following informalities: typographical errors. The term "sulphur" in the lines 11, 21, 27, and 35 of claim 1 should be corrected to --sulfur. In addition, the same typographical errors and other misspellings should be corrected in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of the formula I; including enantiomers, diastereomers, N-oxides and pharmaceutically acceptable salts thereof; the specification is not enabled for *solvates, esters, polymorphs, or metabolites* thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the

presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

The Nature of the Invention**:**

The instant invention is drawn to substituted azabicyclo hexane derevative compounds defined by formula I and all pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, or metabolites thereof.

The state of the prior art and the predictability or lack thereof in the art

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact and generally stable format to store an API or a drug product. Understanding and controlling the solid-state chemistry of APIs, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. APIs can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of

other solid forms such as polymorphs and solvates are not so common as to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate super-saturation and promote crystallization (Morissette *et al.,* Advanced Drug Delivery Reviews, vol. 56, pages 275-300, 2004).

For instance, solvates, at the time the invention was made, were known to exist, and many had been documented, but the level of skill in the art had not progressed to such an extent that the preparation of those solvates other than hydrates was routine or simple. The following references address the state of the art with respect to crystalline forms of organic compounds, formation of solvates of organic compounds, and the lack of predictability thereof:

Vippagunta *et al.*, "Crystalline Solids", Advanced Drug Delivery Reviews, vol. 48, pages 3-26 (2001).

Gavezzotti, "Are Crystal Structures Predictable?", Accounts of Chemical Research, vol. 27, pages 309-314 (1994).

First, it is evident from both of the references that formation of specific crystalline forms, and more particularly, solvates, is highly unpredictable. See Gavezzotti, page 309, the first sentence, and page 312, point #8; also see Vippagunta et al, page 11, "Prediction of Polymorphs" and page 18 "Prediction of the formation of hydrates and solvates". Because the formation of solvates is unpredictable, even the relatively high level of skill possessed by one of ordinary skill

in the art is not enough to render preparation of solvates routine. Each solvate of each compound must be experimentally prepared, by a trial and error process (since the conditions necessary for the formation cannot be predicted), and all of the factors relevant to each individual compound's ability to crystallize must be studied. These factors are identified in points #1-7 of the Gavezzotti reference. The preparation of each single claimed solvate represents a significant undertaking in the areas of preparative organic chemistry, physical chemistry, and crystallographic measurements.

In addition, the phenomenon of polymorphism, in the crystallization of organic compounds, is of crucial importance to the pharmaceutical industry. Two polymorphs of the same drug molecule may have different physical properties: e.g. solubility, bioavailability, melting points, density, hardness, or color; and may have dramatically different properties that effect the scale-up process. Due to the differences between polymorphs, the drug regulatory authorities (e.g. the FDA) are increasingly demanding more information about potential drug products before granting approval. The conditions under which polymorphs interconvert is also of crucial importance, particularly when drugs may encounter exposure to changes in temperature, pressure, and relative humidity during processes such as drying, granulation, milling, compression, and storage. Therefore, for these reasons, the state of the prior art is one of unpredictability. The science of crystallization has evolved such that said differences in properties implies patentable distinctiveness between polymorphs.

Amount of direction/guidance & presence or absence of working examples

There is guidance for the preparation of the compounds in the specification; however, no direction or guidance is present in the instant specification for the preparation of solvates, esters, polymorphs, and metabolites for the compounds of formula I. Also, there are no working examples present in the disclosure for solvates, esters, polymorphs, and metabolites for the compounds of formula I. Therefore, one of skill in the art would be required to identify the correct solvent system and crystallization technique for each compound and, further, identify the similarities and differences between crystals and corresponding spectral data for each compound (polymorph) in order to determine what is being claimed.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include compounds of formula I, and all pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, or metabolites thereof.

The quantity of experimentation necessary

While the level of the skill in the pharmaceutical arts is high, it would require undue experimentation of one of ordinary skill in the art to prepare any solvates, esters, polymorphs, or metabolites of a compound according to formula I as instantly claimed. The science of crystallization has evolved such that, without guidance or working examples for polymorphs in the specification, the claims lack enablement.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Allowable Subject Matter

Claim 2 is allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 8:00-5:00 Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BONG-SOOK BAEK
Examiner, Art Unit 1614

Bbs

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614